EVALUATION OF THE ENVIRONMENTAL TOXICANTS VINYL CHLORIDE (VC) AND VINYLIDENE CHLORIDE (VDC)

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ABSTRACT

We have continued to study the inhalation toxicity of various levels of vinyl chloride (VC) and one level of vinylidene chloride (VDC) in rats and mice.

At the end of 6 months, rats of both sexes exposed to 50, 250, or 1,000 ppm of VC or 55 ppm of VDC, 6 hours a day, 5 days a week, did not show any significant adverse effects on various clinical laboratory data or cause any apparent gross or microscopic lesions. The weight gains of rats exposed to VDC were less than those of the controls.

Exposure to 50, 250, or 1,000 ppm of VC caused a number of deaths or early terminations in mice during the 21st to 26th week. The clinical signs in these mice included rough hair coat, lethargy, anorexia, and sudden weight loss. The high level caused changes in the peripheral blood elements including decreased hematocrit, hemoglobin concentration and/or erythrocyte count, and neutrophilia with a corresponding lymphopenia. The macrophage count in the lung washings was also elevated. All three levels caused acinar proliferation and/or bronchiolar adenoma; the middle and high level also caused angiosarcoma in the liver and/or mammary gland, ductular adenocarcinoma, and squamous cell and anaplastic carcinoma in the mammary gland. The squamous cell and anaplastic carcinomas metastasized to the lung. The incidence and severity of these tumors were in direct proportion to the levels of VC. In addition, malignant lymphoma occurred in the heart, lung, liver, spleen and kidney of one mouse exposed to the low level, and infiltrated the cervical tissue surrounding the trachea, blood vessels and esophagus of one mouse exposed to the high level. There was also a hemangioma in the connective tissue attached to the salivary gland of one mouse exposed to the high level. The tumors were responsible for deaths or early terminations of some mice. At 250 or 1,000 ppm of VC, nearly all mice that died or were terminated during the 21st to 26th weeks had tumors in one or more tissues. Exposure to the high level of VC also caused other lesions in the liver of some mice which were probably associated with angiosarcoma; these included infiltration of nucleated erythrocytes, focal degeneration with necrosis, and infiltration of inflammatory cells in the sinusoids and parenchyma.

Exposure to 55 ppm of VDC for up to 6 months in mice did not cause any adverse signs, including changes in laboratory data or macrophage counts in the lung washings. At the end of 6 months, one male of the eight mice which were terminated had a mild bronchiolar adenoma and two other males had mild acinar proliferation in the lung.

IV. DISCUSSION AND CONCLUSIONS

A. Rats

Exposure of rats of both sexes at 6 hours/day and 5 days/week for up to 6 months to 50, 250, or 1,000 ppm of VC or 55 ppm of VDC did not cause any serious adverse effects. The weight gains of the female rats exposed to 55 ppm of VDC were less than those of the controls during the 6th month. The laboratory results, including hematology, clinical blood chemistry, serum immunoglobins, serum proteins, and macrophage counts in lung washings were not apparently affected. The cytogenetic effects as measured by chromosomal changes in bone marrow cultures are under evaluation. Collagen content in the liver and lung of these rats was not apparently altered. Exposure to VC or VDC did not cause any apparent changes in organ weights nor cause any lesions.

B. Mice

1. Vinyl Chloride

Exposure to various levels of VC caused a number of deaths in mice between the 21st and 26th weeks. There were two deaths in the group exposed to 50 ppm, three early terminations in the group exposed to 250 ppm, and four deaths in the group exposed to 1,000 ppm. Clinical signs in these mice included rough hair coat, lethargy, anorexia, and sudden weight loss. One female exposed to the middle level and three females exposed to the high level had tumors in the mammary gland which were from white to gray to dark red in color.

Exposure to the high level of VC caused some changes in the peripheral blood elements. There were decreases in hematocrit, hemoglobin concentration and/or erythrocyte count. Neutrophilia with a corresponding lymphopenia occurred. These changes were not seen in the control mice or in mice exposed to 1,000 ppm of VC for 1, 2, or 3 months.[2/] The macrophage count in the lung washings of mice of both sexes exposed to the high level was elevated. Since macrophage counts were not performed in mice exposed to the low or middle level, the possibility of a dose response relationship cannot be assessed. Exposure to various levels of VC did not cause any other apparent changes in peripheral blood elements or clinical blood chemistry tests. As for rats, the cytogenetic effects as measured by chromosmal changes in the bone marrow cultures are under evaluation.

Gross and microscopic examinations revealed that 50, 250, or 1,000 ppm of VC caused acinar proliferation and/or bronchiolar adenoma in the lung. The middle and high level also caused angiosarcoma in the liver and various tumors in the mammary gland. The angiosarcoma was also found in the mammary

gland of two females and hemangioma in the connective tissue adjacent to the salivary gland of one male exposed to the high level. The pathogenesis or sequence of changes for the various tumors in the mammary gland is complex. Whether the tumors started at first as ductular adenocarcinoma and then underwent a metaplastic change to squamous cell and anaplastic carcinomas, or all tumors started simultaneously is questionable. However, the squamous cell and anaplastic carcinomas did metastasize to the lung, suggesting a strong malignancy of the neoplasms. In addition, a marked, diffuse malignant lymphoma was found in the heart, lung, liver, spleen and kidney of one mouse exposed to the low level of VC and a malignant lymphoma infiltrated the cervical tissue surrounding the trachea, blood vessels and esophagus of one mouse exposed to the high level. Between the 5th and 6th months the various tumors occurred in five of 10 mice necropsied at 50 ppm, 10 of 11 mice necropsied at 250 ppm, and all 12 mice necropsied at 1,000 ppm. The severity of these tumors in the lung, liver, and mammary gland was also in direct proportion to the exposure level of VC. These tumors were responsible for the various deaths and early terminations of some mice.

Exposure to the high level of VC also caused other lesions, probably associated with angiosarcoma, in the liver of some mice. These lesions were infiltration of nucleated erythrocytes, focal degeneration and necrosis, and infiltration of inflammatory cells in the sinusoids and parenchyma. Intranuclear inclusions increased in the hepatic cells of two mice exposed to the high level of VC. The significance of this increase as related to the treatment is questionable.

2. Vinylidene Chloride

Mice exposed to 55 ppm of VDC for up to 6 months did not show any adverse signs, any changes in laboratory data or macrophage counts in the lung washings. Cytogenetic effects are under evaluation. One male of eight mice terminated at the end of 6 months had a mild bronchiolar adenoma. Two other males had mild acinar proliferation in the lung. These three and another male also had increased intranuclear inclusions in the hepatic cells. The clinical significance of this increase is not understood.